Comments on the Criteria Document for Particulate Matter Air Pollution

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This report contains three documents with comments on the US Environmental Protection Agency Draft Criteria Document for Particulate Matter Air Pollution. The first document is an article for the bulletins of the International Environmetric Society and the American Statistical Association Section on Statistics and the Environment, written by Richard Smith at the University of North Carolina and Peter Guttorp of the University of Washington. The same authors are joined by Lianne Sheppard, also of the University of Washington, in a formal comment submitted to the EPA review process. Finally, Guttorp and Sheppard together with Thomas Lumley and Naomi Ishikawa (also University of Washington) present a another submission to the Criteria Document review.

The matter of particulates and health

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On April 11, the US Environmental Protection Agency issued their latest review of the scientific literature on particulate matter air pollution. The document, called *Air Quality Criteria for Particulate Matter*, is the first step in the process of setting air quality standards in the United States. Once the criteria document is made final, EPA staff produces a document with recommendations to the Administrator of the EPA, who then announces any changes in the air quality standards that may be called for on the basis of the two documents. While the staff document reflects current thinking within the agency, the criteria document is supposed to be an objective and comprehensive review of current scientific thinking in the area.

The document, which is open to public review until July 12, 2001, consists of two volumes (chapters 1-5 and 6-9, respectively), which can be downloaded from the EPA web site at http://www.epa.gov/ncea/partmatt.htm where instructions for public comments can be found.

After the brief general introduction in Chapter 1, Chapters 2 and 3 provide background information on physical and chemical properties of PM and related compounds; sources and emissions; atmospheric transport; transformation and fate of PM; methods for the collection and measurement of PM; and ambient air concentrations; Chapter 4 describes PM environmental effects on vegetation and ecosystems, impacts on man-made materials and visibility, and relationships to global climate change processes; and Chapter 5 contains factors affecting exposure of the general population. Chapters 6 through 8 evaluate information concerning the health effects of PM. Chapter 6 discusses epidemiological studies. Chapter 7 discusses dosimeter of inhaled particles in the respiratory tract. Chapter 8 assesses information on the toxicology of specific types of PM constituents, including laboratory animal studies and controlled human exposure studies. Chapter 9 integrates key information on exposure, dosimetry, and critical health risk issues derived from studies reviewed in the prior chapters. The Executive Summary is to be incorporated at the end of Volume II.

The basic conclusion of the PM criteria document is that particulate matter air pollution has significant effect on mortality and morbidity, particularly on elderly individuals. The document, however, fails to take into account much of the recent statistical literature questioning the validity of the methodology used in many of the studies upon which the conclusion is based. For example, a special issue of *Environmetrics* (vol. 11, issue 6, 2000) on statistical analysis of PM data contained three papers showing the sensitivity of these analyses to model choice, in particular lag structure and air pollution covariates. In a study reanalyzing Seattle $PM_{2.5}$ (particles with average size below 2.5 μm) data and asthma hospital admissions, Lumley and Sheppard (2000) find that the bias due to model selection (choosing between only seven models), the log relative risk estimated from the data is about twice the mean bias in simulated control analyses, and the estimate falls at the 90th percentile of the bias distribution in the control analyses. Thus in studying the weak associations between PM and health outcomes, it is important to take into account biases that normally could safely be ignored. Smith et al. (2000) reanalyzed regression models for air pollution and daily mortality in Birmingham, Alabama, demonstrating the sensitivity of the analysis to the definition of an exposure measure for lagged PM_{10} values, and that there is little evidence of an effect at low levels of air pollution. Clyde (2000) analyzed the same data using Bayesian model averaging, and obtained results that were quite sensitive to prior assumptions. The original study of these data by Schwartz (1993) obtained a relative risk of 1.11. The posterior probability of a risk that large or larger in Clyde's analysis is between 0.007 and 0.0042, depending on the choice of prior.

Many studies have considered other pollutants besides PM, but too often the emphasis has been on how the other pollutants affect the PM coefficient (the co-pollutant problem) rather than starting out from the assumption that there are several pollutants that could possibly explain the mortality effects and we should treat them on equal footing when it comes to identifying potentially causal relationships. Where this has been done, the results are mixed, For example, the Health Effects Institute reanalysis (Krewski et al., 2000) of the Harvard six-cities study (Dockery et al, 1993) found that when treated on an equal-footing basis, SO_2 has a stronger association with health than PM. The PM criteria document implies that this could be because SO_2 is really a precursor to sulfate particles, but it needs to be emphasized that this is hypothesis, not a verifiable conclusion of the epidemiological analysis. Furthermore, different areas of the United States have different compositions of particulate matter, so regional differences may partly be explained by the different pollutant mixtures.

It is important that the environmental statistics community pays attention to the literature review in EPA's criteria document. We feel that the document takes a cavalier attitude towards statistical interpretation issues, which go way beyond mere sensitivity of the results of epidemiological analyses to different kinds of analysis. Large questions of uncertainty and more broadly of variability (e.g. across subpopulations, spatial regions, seasons etc.) are of major concern in ascribing an overall cause and effect relationship, but the document is written in such a way as to imply that none of these issues ultimately affect the conclusions.

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Comments on the PM Criteria Document

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1 Introduction

This paper has been prepared as part of the public commentary process on the second external review draft of the Particulate Matter Criteria Document (EPA, 2001). The Criteria Document was made available for public review on April 11, 2001, and there is a 90-day period during which anyone can submit comments on it. The Criteria Document is an important part of the regulatory process which will lead to the establishment of a new particulate matter standard, and is supposed to represent an impartial review of the scientific literature. Most of our comments concern Chapter 6, "Epidemiology of Human Health Effects from Ambient Particulate Matter", though they are also relevant to Chapter 9,"Integrative Synthesis...", to the extent that the latter chapter draws on material in the former. Where possible, we have tried to refer to specific passages or pages in the Criteria Document, though our most serious reservations do not concern the way the document has treated individual papers that it has reviewed, so much as the overall approach that it has taken. Most of the published studies in this field of research have demonstrated a positive association between increased levels of particulate air pollution and adverse human health outcomes (mortality and morbidity). However, there are many questions of scientific interpretation that must be addressed before these studies can reasonably be said to justify tightened standards and increased regulation of ambient particulate matter. Many of these scientific interpretation issues are of a statistical nature.

In other words, they concern matters such as the design of a sampling scheme, the choice among different methods of statistical analysis, and the statistical interpretation of the results of an analysis. In general, we find that throughout Chapter 6, these statistical issues have been dealt with very poorly or ignored altogether. Nevertheless, there are by now a substantial number of papers in the published, refereed scientific literature that address statistical issues associated with particulate matter epidemiology. Some of these papers have been omitted entirely from the review, while others that are included in the Criteria Document have only been dealt with cursorily or in a manner that ignores their statistical content.

The remainder of this discussion is set our as follows. Sections 2 and 3 are primarily intended to fill in gaps in the CD. Section 2 reviews a special issue of the statistical journal *Environmetrics* on statistical analysis of particulate matter air pollution data. For some reason this special issue, the production of which was part of an EPA-funded effort to assess statistical aspects of the PM question, has been left out of the document. The very brief Section 3 aims to clarify some points concerning one of our papers which is described in the CD. These two sections are largely intended to fill in gaps in the current CD. Section 4 is a much broader review of one of the main methodological techniques used in the current PM literature, time series analyses of ambient PM exposure against either mortality or morbidity outcomes (the present review is primarily concerned with mortality studies). In this, we review a number of the methodological issues raised by these analyses, including the combination of data from different cities (the main purpose of the NMMAPS study), publication bias, the effects of model selection, non-linear dose-response relationships and co-pollutants. Section 5 is a similar review for the other main form of research in this field, cohort studies of long-term effect. Finally, Section 6 summarizes our conclusions. Overall, we believe that for both the time series analyses and the cohort studies, the PM Criteria Document has failed to perform a remotely adequate job of summarizing the available literature in a manner that would allow true appreciation of the complex issues that these studies raise.

2 Environmetrics special issue

A special issue of the environmental statistics journal Environmetrics (vol. 11, Number 6, November/December 2000) was dedicated to statistical aspects of PM air pollution. Although substantial efforts were made to assure that these articles were made available to the PM CD staff in time for the original June deadline, and the issue appeared before the end of the year, these papers have not been taken into account in the CD. We describe the papers in the volume briefly below.

2.1 Sun et al. (2000)

The authors set forth a spatio-temporal model for daily PM_{10} in the Greater Vancouver area in British Columbia. The temporal structure is described by a single autoregressive model of order 1 for all stations. There is no evidence of leakage of correlation from space to time, i.e., the spatial correlation of the raw data and that of the residuals from the time series model are roughly the same. This is in contradistinction to the case of hourly data, where this type of leakage is serious. The spatial correlation by itself is, however, found to be heterogeneous. The resulting model is used for Bayesian prediction of the underlying PM_{10} field in a dense grid of points. The authors point out that the common assumption of spatial stationarity (or homogeneity) is violated in this case, as is quite common in environmental applications.

Interpolation of PM_{10} fields between monitoring stations is of potential importance in assessing the overall societal impact of new air pollution standards. In this paper, the proposed methodology performed well when evaluated using cross-validation, and this to some extent justified the rather complex approach taken (involving a heterogeneous model and hierarchical structure for the spatial dependence, in contrast to a simple geostatistical approach such as kriging). On the other hand, they noted some caveats in their approach, for example, that the interpolated spatial surfaces are very irregular (which complicates the interpretation) and that the model does not seem to do so well in predicting extreme levels of PM_{10}.

2.2 Dewanji and Moolgavkar (2000)

A point process model for recurrent events is applied to hospital admissions for chronic respiratory disease in King County, Washington, over the years 1990-1995. These data have also been analyzed by Moolgavkar et al (2000). The analysis uses different temporal stratifications (varying from no stratification to half months), as well as pollution data on PM_{10}, CO and very fine particles (nephelometry). Temperature was taken into account either using a linear model or a cubic polynomial. All the pollutants are associated with hospital admissions. The effect of PM is stronger than that of CO in multi-pollutant models, in contrast to the previous analysis by Moolgavkar (2000). The effect of temporal stratification, even fairly coarse, is substantial, and decreases the effect estimates compared to those from the non-stratified model.

2.3 Lumley and Levy (2000)

The case-crossover design, which is commonly used in air pollution health effect studies, relies on a strong temporal stationarity assumption. This can be eliminated by using short enough time-frames. The standard analysis, namely conditional logistic regression models as in case-control studies, produces a persistent bias, which is due to a false analogy between the two designs. There are several reasons for this: in case-crossover studies the exposures are autocorrelated over time, while in a matched case-control study the exposures are independent. Two cases that occur on the same day will have the same (or very similar) exposure measures in case-crossover studies, while this constraint between strata does not occur in case-control studies. Finally, in a matched case-control study the stratification depends only on covariates and not on the response, while in a case- crossover study the stratification depends on the response. A simulation study indicated that for data similar to Seattle air pollution data, the degree of bias in this case was not much larger than the finite-sample bias. However, adjustment for meteorological factors or co-pollutants may introduce additional bias.

2.4 Lumley and Sheppard (2000)

The effect of selecting lags on the resulting model for particulate matter health effects is one of the main issues in model selection. Using simulated data with parameters similar to a Seattle $PM_{2.5}$- series, the bias resulting from the selection is shown to be similar in size to the relative risk estimates from the measured data. More precisely, the log relative risk from the measured Seattle data is about twice the mean bias in the simulated control data, and the published estimate of relative risk is only at the 90th percentile of the bias distribution in these control analyses. The selection rule used was to choose the lag (between 0 and 6) with the largest estimated relative risk. In comparisons to real data from Seattle for other years, and from Portland, OR, with similar weather patterns to Seattle, similar bias issues appeared.

2.5 Smith et al. (2000)

Many ad hoc decisions go into model selection in air pollution health effects studies. The effect of some of these decisions on relative risk estimates for Birmingham, AL, PM_{10} data, previously analyzed by Schwartz (1993) and others, is illustrated. The response variable is non-accidental mortality. Specifically, the selection of meteorological variables, the selection of an exposure variable (as a weighted average of lagged PM values), and the possibility of nonlinear effects, such as threshold effects, are investigated. The results are sensitive to the inclusion of humidity in addition to temperature. This inclusion decreases the resulting PM_{10} coefficient. The model is highly sensitive to the definition of an exposure measure. For example, when lags 0-4 were averaged, there was no significant effect. In an attempt to account for a nonlinear PM-mortality effect, there appeared to be little effect of exposure below 80 $\mu g/m^3$, and a threshold analysis (as well as a generalized additive models approach) supported the conclusion that the main effect is at higher values of PM. Although this paper was based on an intensive analysis of a single data set (in contrast to other studies, such as NMMAPS analysis, which combined data form many cities), it demonstrated the very wide range of interpretations that are possible using alternative, but statistically valid, analyses of the same data.

2.6 Clyde (2000)

A more systematic analysis of model choice is obtained using Bayesian Model Averaging. The same Birmingham, AL, data as analyzed by Smith et al. (2000) were used. Several different calibrated information criterion priors were tried, in which models with large numbers of parameters are penalized to various degrees. After taking out a baseline trend (estimated using a GLM estimate with a 30-knot thin- plate smoothing spline), 7860 models were selected for use in model averaging. These included lags 0-3 of a daily monitor PM_{10}, an area-wide average PM_{10} value with the same lags, temperature (daily extremes and average) lagged 0-2 days, humidity (dew point, relative humidity min and max, average specific humidity) lagged 0-2, and atmospheric pressure, lagged 0-2. The model choice is sensitive to the specification of calibrated information criterion priors, in particular disagreeing as to whether different PM_{10} variables should be included or not. For example, some PM_{10} variable is included in all the top 25 AIC models, but only in about 1/3 of the top BIC models. Both approaches give a relative risk estimate of about 1.05 (to be compared to Schwartz value of 1.11 for a 100 unit increase), with credibility intervals of (0.94,1.17) for the AIC prior and (0.99,1.11) for the BIC prior. A validation study in which left out data were predicted using the different priors favored Bayesian model averaging with BIC prior over model selection (picking the best model) with BIC or any approach with AIC.

2.7 Remaining papers

The three remaining papers in this volume are Cox (2000), Phelan (2000) and Sheppard and Damian (2000). The paper by Cox is a summary of presentations and discussions at the PM workshop at the National Research Center for Statistics and the Environment at the University of Washington in Autumn of 1998. Phelan outlines a stochastic process approach to cost-benefit analysis of air pollution regulation, and Sheppard and Damian present a methodological approach to combining ecological and individual-level data in the analysis of air pollution

3 Two points of clarification about Phoenix

The CD refers at a number of places to two papers of ours based on data from Phoenix, AZ. We would like to clarify some issues related to the paper Smith *et al.* (2000).

The reference to this paper in Table 6-1 (page 6-23) notes the absence of a specific estimate for the fine and coarse particles effects. The estimates are as follows (for the same analyses as those actually reported in the paper). Translated into a relative risk for a 25 μg/m^3 increase of either fine ($PM_{2.5}$) or coarse ($PM_{10-2.5}$) particles, the RR for coarse particles is 1.046 (i.e. 4.6% increase in mortality) with 95% CI (1.019,1.074). The corresponding results for fine particles are 0.993 (0.885, 1.109). As noted in the paper, the results are for different populations, city mortality data being used for the fine particles analysis and region-wide data for coarse particles. These numbers may also make it possible to compare the results of the paper with others depicted in Fig. 6-4, page 6-53.

Table 6-2 on page 6-51 also notes the absence from Smith *et al.* (2000a) of statistics related to mean levels of PM_{10} and $PM_{2.5}$. In the data set we used for Phoenix, over the time period for which deaths were available (2/1/95 to 12/31/97), the mean level of $PM_{2.5}$ was 13.2 μg/m^3, the mean ratio of $PM_{2.5}$ to PM_{10} was 0.28, and the value of r, the correlation coefficient between $PM_{2.5}$ and $PM_{10-2.5}$, was 0.68. For three-day aggregate values, the mean and mean ratio are virtually the same, but the correlation coefficient increases to 0.74.

4 Time series analyses

In this section, we review several issues related to time series analyses of PM data, concentrating on those that take mortality as an endpoint.

4.1 The NMMAPS study

One of the most significant new developments in particulate matter research since the 1996 PM CD is the NMMAPS study (Samet *et al.* 2000a,b) which has combined evidence from initially 20, and in later parts of the report 90, of the largest cities in the U.S. This work has, naturally, been given considerable attention to the CD, though with very little attention to the actual methodology involved. Given that we believe this is very important to the interpretation of the results, the following comments are concerned primarily with the methodology rather than the results of the NMMAPS reports.

The simplest approach to combining regression estimates from different cities is a meta-analysis in which the results are weighted with weights inversely proportional to the variance of the individual city estimates. This approach can be criticized as not allowing for random effects between the cities — in effect, a simple meta-analysis assumes that the effect being measured is the same in all cities, whereas in fact, one would expect the effects to be different in different cities. (To give just one among many reasons why, it is obviously the case that the composition of particulate matter varies by city, and there is growing evidence that PM composition has an important influence on health effects, though the precise nature of that influence is far from being well understood. If

PM effects are analyzed city by city, without explicitly taking PM composition into account, one has to expect that the results will differ to a greater extent that what would be explained by variability in the individual regressions.) The hierarchical model analysis introduced in the NMMAPS report and in Dominici *et al.* (2000) allows for random effects, but there are potentially many different ways of specifying such a model. An even more radical, but potentially very important, extension of the analysis is to allow for spatial dependence among the cities. However, after making a good start to the spatial analysis (Part I, p. 68), there is actually very little discussion of the spatial model itself (for example, do spatial correlations based on the fitted model actually correspond to observed spatial correlations in the data?), and in Part II, it is apparently abandoned in favor of a somewhat simpler, but possibly less realistic, regional analysis.

From a modern perspective, all these models may be estimated using Bayesian Hierarchical Models, but different specifications of the models (e.g. different prior distributions) do lead to different results, and there is still only an incomplete understanding on how the prior specification influences the properties of the resulting estimators. The methods of Dominici, Samet and Zeger are as good as anything anyone else has derived, but there is not a full understanding of their properties.

One example of the contrast produced among different prior distributions and modeling approaches is Table 4 of Part I (page 71), where the posterior probabilities that the overall effect is positive are notably lower when the spatial model is adopted than under either the univariate or bivariate non-spatial models. The most likely explanation of this is that if spatial dependence is really present but is ignored, as in the univariate and bivariate models, then the posterior variances of the parameter estimates are underestimated, resulting in too high a posterior probability (the same positive posterior mean, but a larger posterior variance, would lead to a smaller posterior probability of a positive effect, assuming no substantial change in the shape of the posterior distribution between the two analyses). In Table 4, even under the spatial model, all the posterior probabilities are still over 0.8, but the fact that there is this difference between the spatial and non-spatial models makes it more disturbing that the spatial model has not been pursued more vigorously in Part II of the report.

The weighted regression (or meta-analysis) approach is also mentioned at a number of places and specifically developed for the morbidity analysis in Part II (pages 32–35 for the basic methodology). This is a simpler form of the non-spatial hierarchical models analysis, and should lead to fairly similar results as the Bayesian approach, as the authors claim at several points. The potential disadvantages of the weighted regression approach are (i) the final estimates and standard errors do not fully allow for uncertainty in estimating the variance components, and (ii) the method of estimating the variance components, in column 2 of page 34, is less efficient than maximum likelihood or Bayes — note, in particular, the possibility that $\hat{\Omega} = 0$. From various comparisons made in the text, it appears that these issues do not affect the results too much, but they might if conmpared with a fully spatial analysis in Part II.

In conclusion, we believe that the hierarchical modeling approach is sound, and a major new contribution to the methodology of particulate matter research. Our main concern is whether the authors have really explored enough different versions of the model, and especially, that they might not have gone far enough in the spatial analysis.

4.2 Publication bias

In section 6.4.4 (lines 26, 27 of p. 6-238), the CD explicitly claims that it is reasonable to select the most significant lag among a set of possible lags even though such a practice may bias the chance of finding a significant association. This statement is made in spite of evidence of model selection bias that results from this approach in the peer-reviewed literature (e.g. see the specific study examined by Lumley and Sheppard, 2000) and evidence to the contrary that can be compiled from studies reviewed in the CD alone. We now present an analysis of data from the CD that indicates the presence of selection bias in the published literature.

The NMMAPS study can be used as a gold standard against which to assess the presence of publication bias in other PM mortality effect analyses. Among the strengths of NMMAPS relevant for an analysis of publication bias, the data were consistently handled across all cities, city-specific models were specified using the same criteria in each city, and the cities to be included were not specifically selected based on outcome (size is a covariate, not an outcome).

We compare the compilation of city-specific results from NMMAPS (gleaned from Figure 6-1 on page 6-41) with estimates reported in 21 separate references in Table 6-1. To be eligible for this analysis, the paper had to report a total mortality effect estimate for a 50 μg/m^3 increment of PM_{10}, reside in the peer-reviewed literature and represent a distinct analysis or dataset. (Thus, for example, we excluded separate published analyses of the 10 cities analyzed by Schwartz (2000). We did not include Levy (1998) because in our opinion it was based on incomplete work.) All the estimates considered were city-specific with the exception of the Schwartz (2000) 10-city estimate and the Burnett (1998) 8-city estimate. Table 1 shows the included studies, cities, statistical significances (as indicated by the CI), and effect estimates gleaned from Table 6-1 of the CD.

We test the null hypothesis that there is no difference between the NMMAPS collection of results and the independently published set. We can test this hypothesis in two ways: by looking at statistical significance of the results and by considering positive point estimates of excess deaths. In both cases we use a two-sample test of proportions and rely on the asymptotic normality of this statistic. In NMMAPS, 11 out of 88 city-specific estimates were statistically significant (i.e. had confidence intervals that excluded 0) and 63 out of 88 gave positive point estimates for excess deaths. In contrast, out of the 24 separate confidence intervals reported in the 21 references, 19 of 24 were statistically significant.

First author and publication date	City	Statistical significance	Estimate for $50\mu g/m^3$ PM_{10}
Schwartz (2000a)	10 cities	Sig	3.4
Moolgavkar (2000a)	Cook County	-	.5-1
Moolgavkar (2000a)	Maricopa County	-	.25-1
Moolgavkar (2000a)	LA	-	.5
Ostro (1999a)	Cochella Valley	Sig	4.6
Ostro (1999a)	Cochella Valley	NS	2.0
Fairley (1999)	Santa Clara County	-	8
Pope (1999a)	Ogden	Sig	12
Pope (1999a)	Salt Lake City	Sig	2.3
Pope (1999a)	Provo	NS	1.9
Schwartz (2000)	Chicago	Sig	4.5
Lipmann (2000)	Detroit	NS	4.4
Gwynn (2000)	Buffalo	Sig	12
Mar (2000)	Phoenix	Sig	5.4
Tsai (2000)	Newark	Sig	5.7
Tsai (2000)	Camden	NS	11.1
Tsai (2000)	Elizabeth	NS	-4.9
Gamble (1998)	Dallas	NS	-3.6
Burnett (1998a)	8 Canadian Cities	Sig	3.5
Burnett (1998a)	Toronto	Sig	3.5
Wordley (1997)	Birmingham UK	Sig	5.6
Hoek (2000)	Netherlands	Sig	0.9
Ponka (1998)	Helsinki	Sig	18.8
Peters (1999a)	Czech Republic	Sig	4.8
Michelozzi (1998)	Rome	Sig	1.9
Wichmann (2000)	Frankfurt	Sig	6.6
Morgan (1998)	Sydney	Sig	4.7
Ostro (1998)	Bangkok	Sig	5.1

Table 1: Studies including PM_{10} mortality estimates in CD, Table 6.1.

This leads to a z-statistic of 7.29 and resoundingly rejects the null hypothesis of no difference. Similarly, of the 28 separate effect estimates reported, 26 were positive, leading to a z-statistic of 3.09 for this comparison. Again the null hypothesis of no difference is rejected. Thus by relying only on information summarized in the CD, it is reasonable to conclude that the statement on page 6-238 (lines 26-27) is inappropriate.

Since the study of air pollution health effects is no longer in its infancy, it is not appropriate for studies to continue to operate in a hypothesis-generating mode where a priori no single candidate model is preferred and the investigators report the model producing the results most consistent with the prevailing prior hypothesis. The standard of analysis in the epidemiologic health effects literature must shift away from hypothesis generation to hypothesis confirmation. Hypotheses ought to be stated a priori, then tested and reported. Only after this confirmatory analysis can more exploratory secondary analyses be done, analyses that may consider other possible models. Even then recognition of the potential bias due to model selection should be specifically acknowledged in the CD.

4.3 Model selection

From a statistical point of view, the common epidemiological practice of choosing variables (including lagged variables, co-pollutants, etc.) that maximize the resulting effect estimates is a dangerous approach to model selection, particularly when the effect estimates are close to 0 (i.e. RR close to 1). As has been demonstrated in Lumley and Sheppard (2000), the effect of choosing lags for PM_{10} in this fashion has a bias which is of the same order of magnitude as the relative risk being estimated. This, in particular, throws doubt over the results of Sheppard et al. (1999), which on the face of it yielded a convincing case for the effect of PM_{10} and/or CO on the rate of hospital admissions of asthmatic children, since the Lumley and Sheppard simulation study used parameter values corresponding to those in Sheppard et al. (1999). More importantly, it demonstrates through a specific study the magnitude and type of bias that may be operating in all air pollution epidemiologic studies that select the most significant lag after evaluating a set of lags.

Similar selection bias results were illustrated by Smith et al. (2000). Thus, statistically speaking, doubts can be thrown over all studies which do not use an objective information criterion for selecting variables and/or lags. While it could be argued that, e.g., PM_{10} acute health effect generally appear to operate at lag 1 day)the analyses of Clyde (2000) and Clyde et al. (2000) find PM_{10} lag 1 as a strong predictor in most of the models ranked highest be either AIC or BIC, using a Bayesian model averaging procedure), the literature, perhaps due to the variable selection practice mentioned above, does not show substantial agreement as to which lag(s) to use.

While there are several model selection criteria (such as C_p, BIC, AIC, Bayes factors etc.), and no consensus within the statistical community regarding which criterion to use, there is agreement among statisticians that stepwise methods have serious drawbacks in terms of bias. In particular, when the estimated risk effects are very small, the epidemiological selection principle not only leads to bias in the estimates, but also to a false sense of scientific consensus, in that the estimates from models so selected will tend to be more similar than what is actually warranted by the data.

The advantage with the Bayesian model averaging procedure, as used by Clyde (2000) and Clyde et al. (2000), is that several models that are well supported by the data are considered simultaneously, rather than selecting a single *best* model. The standard error of relative risk estimates obtained in this fashion reflect the model selection procedure, while methods selecting a single model tend to ignore the selection, and calculate standard errors as if only the chosen model had been considered. Another feature of Bayesian model averaging is that it is straightforward to incorporate prior beliefs about important lags and variables in the analysis (although Clyde and co- workers have tended to weight all possible models equally). If the data disagree with the prior beliefs, this comes out of the analysis. A drawback, on the other hand, is that the methodology is somewhat sensitive to which criterion is used to rank the models (see Clyde, 2000).

4.4 Non-linear dose-response relations and thresholds

One of the critical questions associated with the translation of epidemiological studies into particulate matter standards is whether the dose-response relationship is linear and whether there is any evidence of a threshold, i.e. a critical level below which there is little or no effect of increasing air pollution on health.

Many of the early studies of PM-health relations were based on levels of PM much higher than those typically observed today. For example, in the notorious "London smog" of December 1952, in which there are estimated to have been 4,000 excess deaths as a result of air pollution, smoke levels reached as high as 3,000 $\mu g/m^3$. Schwartz and Marcus (1990) reported that mean smoke levels in London declined from about 500 $\mu g/m^3$ to about 60 $\mu g/m^3$ over the period 1958–1971, with corresponding decreases in the death rate. (The measure of air pollution used in these studies was "British smoke", which as an extremely rough guide is typically about twice the PM_{10} level.) Schwartz and Marcus were possibly the first authors to claim that health effects actually persisted to the very lowest levels of PM, though their claims were quickly followed by a number of others — Pope (2000) has provided further historical perspective.

The issue, as it appears to us, is not whether very high levels of pollution are responsible for mortality effects — this seems to be established beyond reasonable doubt — but whether the effects really do persist to a level below that of the current PM_{10} standard, which would justify a tighter standard. This requires critical examination of the shape of the dose-response curve across a wide range of dose levels, but particularly at those near to or below the current standard. It is not sufficient to argue that the relationship must be linear unless proved otherwise, though this reasoning is implicit in any hypothesis test that takes a linear relationship as the null hypothesis.

Our own attempts to examine this issue have produced confusing results. Smith *et al.* (2000a) examined both fine and coarse particle effects in Phoenix, concluding that there is a threshold (in the region of 20–25 μg/m^3) for fine particles, but not for coarse particles. (As a side comment on a statement made in the CD, page 6-247 remarks on the fact that the fitted nonlinear relationship for fine particles is roughly V-shaped, being a decreasing function of PM at low PM levels, and questions whether this is biologically plausible. We agree that it is probably not, but we did not claim that the negative slope is statistically significantly different from 0 — the confidence bands drawn in the paper show that it is not. On the other hand, we did quote p-values lower than 0.01 against the hypothesis of an overall linear effect.) Smith *et al.* (2000b) claimed evidence for an increasing slope in the dose-response relationship, and possibly for the existence of a PM_{10} threshold at a level above 50 μg/m^3, in data from Birmingham. On the other hand, the same methods applied to data from Chicago (Smith *et al.* 1999) showed no evidence of a threshold and even a sharply increasing effect in the range 0–20 μg/m^3, a result which is also of questionable biological validity. More broadly, the CD openly acknowledges the difficulty in identifying thresholds, for example on page 6-9, and recognizes that even if thresholds do exist on an individual level, such effects may be masked when aggregated over the population (page 6-246).

Against this background, it is to be welcomed that there are some recent studies, notably Schwartz and Zanobetti (2000) and Daniels *et al.* (2000), that have sought to resolve the issue by combining data from a number of cities. However, we question whether the analyses have yet been taken far enough to establish anything conclusive.

For example, Daniels *et al.* (2000) took the same 20-cities data as in the NMMAPS study, and fitted a log-Poisson regression model including all the usual covariates (current day and 3-day averaged lagged days for temperature and dewpoint, both modeled via cubic splines, long-term trends also modeled by cubic splines, plus day of week and age-group effects), initially treating PM_{10} (a) as a linear effect, but then modifying it to (b) modeling PM_{10} nonlinearly using cubic splines, with fixed knots at 30 and 60 μg/m^3, (c) a threshold model. This analysis was initially conducted on a city-by-city basis, but then combined across cities by a hierarchical models analysis. The form of hierarchical model was to assume that the parameter estimates of interest for city c, $\hat{\phi}_c$ say, are distributed according to $\hat{\phi}_c \sim N[\phi_c, V_c]$ where ϕ_c are the random effects for city c and V_c is a covariance matrix for the estimates at city c (one presumes — in the paper, V_c is not actually defined), while the random effects ϕ_c are drawn independently from $N[\phi, D]$, ϕ and D having flat prior distributions. This defines a hierarchical structure from which one can draw posterior distributions by Gibbs sampling, though many other hierarchical structures are possible, if different assumptions are made for the inter-city effects. This scheme was used for the linear and spline models for the PM-mortality relationship; for the threshold model, noting the difficulty of estimating thresholds in individual cities, the authors did not attempt any hierarchical approach but simply combined the log likelihood across cities, implicitly assuming independence from city to city. Throughout the paper, beyond the direct comparison among approaches (a)–(c), there is no attempt to study the robustness of the conclusions against alternative model specifications, and the justification for the hierarchical model assumptions is not clearly made at all. Given the emphasis made on regional and spatial analyses in earlier analyses of the NMMAPS data, one would have expected some consideration of similar issues here.

Despite these criticisms, the analysis by Daniels *et al.* was a good first stab at the problem. However, as things currently stand the analysis is incomplete, and we anticipate that it will take a number of alternative analyses of the same or similar data before any definitive conclusions can be drawn. This is only to be expected, given the complexity of the issues involved and the number of alternative approaches that are potentially available for estimating non-linear dose-response effects simultaneously in a large number of cities. The analysis by Schwartz and Zanobetti (2000) also used nonlinear dose-response functions and combined data across cities via a meta-analysis approach, but this raises similar issues regarding the sensitivity of the analysis to alternative methods of statistical analysis, especially, alternative approaches to the meta-analysis. The narrowness of the confidence bands in Fig. 2 of Schwartz and Zanobetti, when compared with Fig. 3 of Daniels *et al.*, does lead us to question whether the Schwartz-Zanobetti approach is adequately allowing for inter-city variation.

The results of both papers imply that there is no strong evidence against a linear relationship, at least for all-cause, cardiovascular and respiratory mortality (Daniels *et al.* do suggest the existence of a threshold if cardiovascular and respiratory deaths are excluded), but we do not see these two studies as resolving these very complex issues. Our criticism of the CD (specifically, the section between pages 6-245 and 6-248) is that is has focussed exclusively on the results of these papers and has not paid any attention to the methodology of the analysis. However, without appreciating the methodology that was used, and its strengths and limitations, we do not think it is possible to form an overall scientific judgement of the results. At the very least, the CD should have highlighted the need for more work on these issues.

4.5 Co-Pollutants

The issue of whether co-pollutants need to be included in health effects analyses, or if the analysis becomes cleaner when only one pollutant at the time is included in the analysis, is subject to substantial, and in our view very confused, discussion in the criteria document. It appears that the authors are arguing that since many different co-pollutants tend to be correlated, the uncertainty of the health effects estimates tend to cloud the conclusions. This is only the case if one assumes a priori that particulate matter must have an effect on health independently of other pollutants. This, however, is what the analyses discussed in the document are attempting to investigate, and the conclusions are far from clear-cut.

In the NMMAPS report, The effects of PM_{10} are, generally, not much changed if the gaseous co-pollutants (O_3, SO_2, NO_2 and CO) are included as additional covariates in the models (see, in particular, Fig. 25 on page 27 of Part II). On the other hand, comparisons of PM_{10} for the primary pollutant, with each of the others as a primary pollutant, still does not show clear evidence that PM_{10} is the primary "culprit" as far as pollution-mortality effects are concerned. O_3 effects in summer, and each of the other gases overall, are statistically significant, or very nearly so, in at least one of the analyses reported (Figs. 26–29, pp. 27–28). Note that these analyses are based on the 20 cities, not the 90 cities. It would be of interest to see them repeated for the full 90 cities.

In many US cities ozone is only measured during the "ozone season", which generally does not include the winter (when particulate matter due to wood smoke is prevalent, especially in Western US). This adds substantially to the difficulty of separating out the effects of different pollutants.

The epidemiological evidence of the severity of fine particle health effects is simply not yet available: there is insufficient availability of $PM_{2.5}$ data to draw any firm conclusions. There are several studies in which the PM effects disappear when other pollutants are included in the model. There are also several studies with the opposite result. In our opinion, the most severe problem is that we do not yet have a firm grip on the composition of particulate matter in different parts of the United States. The criteria document authors seem to expect that health effects of particulate matter is a matter only of the size of the particles; not of the chemical composition of the particles. The variety of results with respect to co-pollutants can perhaps be caused by the variety of chemical compositions; this is certainly a likely explanation of the regional variability found in the 90-cities study.

5 Cohort studies

The claim that particulate matter causes long-term effects as well as short-term effects relies almost entirely on three prospective cohort studies, the Harvard Six-Cities Study (HSC — Dockery *et al.* (1993)), the American Cancer Society Study (ACS — Pope *et al.* (1995)) and the Adventist Health Smog Study (AHSMOG — Abbey *et al.* (1999)). The HSC and ACS studies were included in the 1996 PM Criteria Document and, as noted on pages 6-81 and 6-82 of the current draft PMCD (Environmental Protection Agency 2001), raised a number of questions — the four specifically listed there are (1) whether important confounding variables have been omitted, (2) the influence of other atmospheric pollutants besides PM, (3) the evaluation of time scales for long-term exposure effects, and (4) the existence of pollution thresholds.

The most significant new study published since the 1996 PMCD is a major reanalysis of the HSC and ACS studies sponsored by the Health Effects Institute

(Krewski *et al.* (2000)). As a result of these re-analyses, the draft PMCD reports (p. 6-82) that "considerable progress has been made towards addressing further the above issues" and, while admitting that the results of the AHSMOG study have been less decisive, concludes that (p. 6-94) "there is evidence for an association between long-term exposure to PM (especially fine particles) and mortality". The further summary on chapter 9 (especially, section 9.6.2.2, page 9-64) concludes that "One of the most important advances since the 1996 PMCD is the substantial verification and extension of the findings" (of the original HSC and ACS studies).

While we acknowledge that the HEI re-analysis was a very important study that added considerable depth and breadth to the original studies of Dockery *et al.* (1993) and Pope *et al.* (1995), we strongly dispute the implication, evident in the above quotes, that it has cleared up all the problems associated with the earlier studies. The re-analyses identified numerous methodological issues whose resolution is very far from clear at the present time.

We have no dispute with Part I of the HEI re-analysis, which was concerned with an audit of the data sources and verification that the original statistical analyses, as reported by the original authors, would indeed produce the results cited in the original papers. This part of the study was well executed and indeed helped to clarify a number of issues about exactly how the original authors performed their analyses. The comments below all refer to Part II of the re-analysis, which was called a "sensitivity analysis" but in reality went well beyond mere checking of the sensitivity of the results to certain assumptions in the original analyses, being a wholescale re-examination of the methodology that lay behind the study.

5.1 The ecological nature of the studies

The draft PMCD (page 6-2) cites Rothman and Greenland (1998) as classifying four common types of epidemiological study in order of increasing inferential strength, with "ecologic studies" as number 1 (lowest strength of inference), followed by 2. time series studies, 3. longitudinal panel and prospective cohort studies, and 4. case-control studies. The implication is that the cohort studies lie higher up the inferential food chain than the time series studies, and form a good basis for causal inference, though it is admitted that "the use of community-level or estimated exposure data may weaken this advantage, as in time-series studies".

In fact, we would argue that the three studies referred to are *primarily* ecologic studies. They would be convincing if they succeeded in correlating variations in mortality with variations in air pollution exposure *within* a community. But the comparisons they make are *between* communities. Taking HSC as an example, the original analysis employed a Cox proportional hazards analysis using various individual-level covariates (age, sex, smoking history, body-mass index and education level) to compute adjusted mortality rates for each city, and then (Dockery *et al.* (1993), page 1757 recomputed as Krewski *et al.* (2000), p. 76) plotted the resulting mortality rate ratios against mean levels of several air pollutants. For example, Portage, Wisconsin had the lowest adjusted death rate amongst the six cities and Steubenville, Ohio, had the highest; it was also the case that Portage had the lowest and Steubenville the highest of both fine and total particles (with several other pollutants showing a similar pattern).

A "pure" ecologic study would be one which compared the average mortality rates to the average pollutant levels without any adjustment for individual-level covariates. That would have the obvious flaw that differences observed among the six cities could be due to different distributions of those covariates (for example, more smokers in Steubenville than Portage) rather than air pollution effects. Certainly, the HSC study was better than that. But the assertion of a *causal* relationship between air pollution and long-term mortality rates amounts to the statement that there cannot be any other possible cause for these differences. This we would dispute. All the reported relative risks due to air pollution, derived from the HSC study, are based on regression on precisely these six data points.

The re-analysis tried to test these conclusions by including some other covariates in the analysis, such as occupational type and an indicator of population mobility. It was the case, for example, that among the six cities, Steubenville had the highest proportion of the population working in "dirty" occupations. Despite this, associations between total mortality and pollution still remained under the re-analyses, though they did find one curious fact, that the association does not seem to be present among the segment of the population with a post-high-school education (this fact is noted and highlighted in the draft PMCD).

Nevertheless, the fact that the relationship between standardized death rates and mortality was not destroyed by the inclusion of a small number of specific alternative covariates does not mean that the original conclusions have been proved correct. The very weak inferential basis for making causal assertions in this study remains, however many alternative covariates are tested.

5.2 The ACS study

Although the ACS study was not as carefully carried out as the HSC study (for example, the participants were largely volunteers rather than selected by randomization), it involved many more participants (552,138 as against 8,111) and many more cities (a total of 154). (Just as a point for comparison, the AHSMOG study also involved a relatively small sample size, 6,338 subjects, and this fact may be responsible for the inconclusive results of that study.) Although the general points about the ecological nature of the study are just as true of ACS as they are of HSC, with the much larger number of cities, there are many more possibilities for alternative modeling of the inter-city data. Indeed, we would regard the innovations made by the re-analysis team in this respect as one of the major contributions of the entire study.

In the rest of this subsection, we comment on three of these which may all be thought of as addressing, in different ways, the issue of ecological effects, (i) ecologic covariates, (ii) random effects models, and (iii) spatial analyses.

5.2.1 Ecologic covariates

As an attempt to evaluate whether inter-city differences in mortality rates could be due to other city-level variates than particulate matter pollution, the re-analysis developed a suite of 30 "ecologic covariates" (20 of which were actually used in the analysis). These included demographic and socioeconomic variables (e.g. percentage of whites and blacks, poverty level, mean income), climate and physical environment variables (e.g. mean altitude, mean temperature) and health service indicators (number of physicians, number of hospital beds). They also included alternative air pollution indicators (CO, NO_2, O_3, SO_2). With the ecologic covariates introduced one at a time into the analysis, only two had a substantial impact on the coefficient due to sulfate particles in the total-mortality analysis. These were population mobility and SO_2 (Table 34, p. 180, of Krewski *et al.* (2000)). Moreover, when SO_2 was treated as the primary covariate, the relative risk due to SO_2 was higher than that due to sulfate particles, and unaffected if sulfate particles were also included in the analysis. Other results largely confirmed the same pattern. The re-analysis team also conducted rather limited analyses using multiple ecologic covariates.

The idea of incorporating ecological covariates is evidently a controversial part of the work. The original authors of the ACS study, commenting at the end of the Krewski *et al.* report (page 275), remarked "From the very beginning of the reamalysis, we were opposed to the idea of taking a myriad of ecologic variables and including them as covariates in the models...[In the ACS study] we considered the original work to be a straightforward, clean, elegant way to generate and test a specific well-defined hypothesis".

Of course, it is perfectly true that introducing a very large number of irrelevant covariates has the potential to weaken a genuine effect which is present in the data. But the passage just quoted seems to be denying the possibility of ecological effects. Although imperfect, we believe the ecological covariates analysis was an important part of the re-analysis and, to some extent, was successful in demonstrating that a number of plausible ecological covariates could not in fact explain the differences in mortality rates. We feel that they could have tried multiple regression analyses to a greater extent than they did, recognizing that the differences in mortality could be due to combinations of ecological factors rather than any one factor operating on its own. The interpretation of the two variables that were significant remains open to dispute. Population mobility may be related to educational status, and it was observed earlier that the PM effect does not seem to be present among those if high educational attainment. The findings about SO_2 relate to the whole issue of co-pollutants, to which we return later.

5.2.2 Random effects models

Even if it were correct that the differences in air pollution were the major factor explaining differences among mortality rates in the different cities, it would be scarcely credible that air pollution could be the only effect. Even after adjusting for air pollution, one would expect to see differences among the cities that go beyond individual-level variation. One of the methodological contributions of the re-analysis was an analysis that allowed for random effects in cities to explain other sources of variation. The results (Table 50, p. 213) showed no great sensitivity in the point estimates and confidence intervals when the random effects model was included. However, it was noted by the Review Panel that the estimated values of τ, the standard deviation of the city random effect, was comparable with the uncertainty in the estimated PM effect, and this in turn could complicate the interpretation of the PM effect. "If a large component of the variance is unexplained in the data, a model including sufficient variables to identify this residual variation might produce different regression coefficients for the variable of interest" (Krewski *et al.* (2000), page 259).

5.2.3 Spatial analyses

Going beyond a simple random effects model, a major finding of the HEI re-analysis was that there seems to be substantial spatial correlation among both air pollution and adjusted mortality rates. Although this could be a separate issue from that of "ecological bias", they are connected in the sense that spatial correlation implies there are other sources of inter-city variation than pure variation in the level of air pollution. In a sense, the spatial correlation that remains after known covariates are taken into account can be regarded as representing additional variability due to unknown covariates.

Spatial correlation was detected by drawing maps, by formal tests of spatial correlation (Moran's I and G tests), and by performing regression analyses that adjusted for spatial correlation. Since our main concern in this commentary is the possible effect of spatial correlation on the conclusions about particulates and mortality, we concentrate on the third of these issues. Within the framework of spatially adjusted regression analyses, three kinds of analysis were carried out that tried to allow for spatial correlation in the regression. The first of these was based on a simple regional classification with random effects due to region. This analysis, while certainly a good first start on the problem, cannot be expected to adjust for all the effects of spatial correlation. The second analysis was based on first passing the data through a spatial filter designed to achieve approximate uncorrelatedness, and then regressing the filtered data. Although it seems promising, this method has uncertain properties —for example, the definition of the spatial filter is *ad hoc* and, even if it were derived from a specific spatial autocorrelation function, no allowance is made for the effects of estimating the autocorrelation structure.

The third analysis that attempts to adjust the regression for the effects of spatial correlation is one based on a specific spatial model. The model selected by the authors of the study was the SAR (simultaneous autoregressive) model, in which the map of the US was covered by so-called Thiessen polygons, one city in each polygon, and two cities considered to be "neighbors" if their polygons touched each other. The dependence between neighboring cities is represented by a correlation parameter ρ. There are various reasons why this model is not especially suitable for the kind of spatial dependence being studied. The tiling of the map does not correspond to any physical model of the spatial variation, and has some counterintuitive properties, e.g. if new cities were added to the study the Thiessen polygons and hence the assumed correlations would change, but it seems implausible that the correlation between two cities in the study would change according to which additional cities were also included. The model is also oversimplified in that a single parameter ρ is assumed to characterize the spatial dependence across the entire country. In our view, it would be more appropriate to use a continuous random field model of the kind common in geostatistics and environmetrics, and the authors might also have explored the possibility of nonstationarity in the spatial dependence structure.

In spite of the incomplete nature of the spatial analysis, it did have a significant impact on the results. For example, in an analysis including both sulfate particles and SO_2 (Krewski *et al.* (2000), pp. 210–211), the RR for sulfate dropped from 1.20 to 1.08 (95% CI: 0.91 to 1.28) though that for SO_2 was less affected (RR from 1.35 to 1.31; CI 1.12 to 1.50). If such a substantial change is possible through only a one-parameter addition to the model, it can only be speculated what would happen with more realistic spatial models.

5.3 Threshold effects

As noted in our introduction to this section, one of the issues identified in the 1996 PMCD as an issue needing clarification (in connection with cohort studies) was that of threshold effects. Unfortunately, the re-analysis shed little light on that issue.

Although there may not be evidence for a strict "threshold" in PM-mortality studies, there may well be an nonlinear dose-response effect, with the incremental effect due to PM changes being higher at high levels of PM than at low levels. The re-analysis investigated this issue at two different points.

First, Fig. 6 of the report (Krewski *et al.* (2000), page 162) shows standardized residuals of mortality against either sulfate concentration or fine particles, for all-cause mortality, for cardiopulmonary mortality, and for lung cancer mortality. All six figures are of similar shape. A widely dispersed scatterplot has been smoothed using cubic splines, and the resulting smoothed curve superimposed on the scatterplot with confidence bands. The shapes of the fitted curves vary, and e.g. for the dependence of all-cause mortality and cardiopulmonary mortality on fine particles actually show a higher slope at low PM levels (10–15 μg/m^3) than higher. However, in all six plots the width of the confidence bands, relative to the total variation in mortality rate, makes it hard to give any definitive conclusion about whether the overall relationship is linear or not.

In contrast, Figs. 10 and 11 on page 175, in which the ordinate is a log hazard ratio but otherwise supposedly conveying the same information as Fig. 6, gives a very different impression — a much more definitive shape to the curve which, in the case of $PM_{2.5}$, shows a statistically significant decrease between about 16 and 21 μg/m^3. We are extremely puzzled about this.

5.4 Co-Pollutants

As noted in our discussion of ecological covariates, SO_2 showed up as a significant variable (though not other atmospheric pollutants that were also considered). Consistently throughout the re-analysis study, when SO_2 and particulates were treated on equal footing, SO_2 came out showing a stronger effect than particles. There is some controversy about the interpretation of this (page 6-86 of the draft PMCD) because the sulfate measurements were complicated by an artifactual component which did appear to influence the results. SO_2 is generally a precursor to sulfate particles and it is quite possible that while it is the particles that have the health effect, it is the SO_2 that is more easily detected and measured, thus creating an apparently stronger effect for SO_2 than for sulfate. However, this is hypothetical: the exclusive focus on particulate matter as a pollutant of interest does not seem to us to be justified by the current epidemiological analyses.

5.5 Are they really measuring long-term effects anyway?

Throughout the discussion of time series and cohort studies, the impression created is "time series studies prove there are short-term effects and cohort studies prove that there are long-term effects". Evidently, "acute effects" deaths are also being included in the cohort studies, and there is no direct way to separate the two.

The draft PMCD (page 9-61) cites the 1996 PMCD that "PM effect size estimates for total mortality indicate that a substantial portion of the deaths reflected cumulative PM impacts above and beyond those exerted by acute exposure events", and goes on to report the "substantial verification and extension" of these findings by the re-analysis. In other words, measure the RR for acute effects using time-series studies, and that for acute and chronic effects combined using cohort studies, and if a significant difference exists, it must be due to chronic effects.

However, even when considering the time series analyses and the cohort analyses separately, there exist substantial difference from one analysis to another due to model selection, and moreover, the estimated RRs, even if statistically significantly greater than 1, always have wide confidence intervals associated with them. To read much interpretation into differences in RR levels from completely different types of analysis does not seem justified.

The re-analysis addressed part of this issue, in the case of the HSC study, by including PM as a time-dependent covariate. For ACS, the study was based on a single PM measurement (from 1982) for each city, and the difficulty with interpreting the actual numerical value of a RR is that the 1982 level may be completely unrepresentative of historical levels of PM, beyond some loose expectation that the most polluted cities in 1982 were probably also the most polluted cities in earlier years. This difficulty has been acknowledged both by the original authors and in the reanalysis. For HSC, some examination of this issue is possible because the study authors did have available historical records of PM (though not as far back as one would like to perform a genuine "lifetime exposures" analysis). When this is included in the model, the effect is considerable: comparing model 5 (treating PM as constant) with model 6 (time dependent) in Table 14 of Krewski *et al.* (2000), the estimated RR drops from 1.31 (95% CI: 1.13-1.52) to 1.16 (1.02-1.32), in effect, a halving of the estimated effect. This kind of sensitivity, to how the historical PM variable is treated, underlines the extreme difficulty of separating short-term and long-term effects in this kind of analysis.

5.6 Summary of cohort re-analysis

It is not our purpose here to criticize the re-analysis itself, which accomplished an enormous amount under intense time pressure. Virtually all the points mentioned here were brought up either by the re-analysis team themselves, or in the HEI Review Panel commentary. The draft PMCD seems to have concluded that the HEI re-analysis ended up confirming all the major claims that were made in the original HSC and ACS analyses. However, careful reading of the re-analysis shows that there are in fact numerous very important issues of methodology and interpretation, to which the re-analysis certainly made significant contributions, but which cannot be considered resolved at the present time. They may never be.

6 Conclusions

One of our concerns about the PM Criteria Document is its failure to cover all relevant literature, and in Section 2 of the present discussion, we have attempted to fill in one of the omissions, concerning the special issue of *Environmetrics* on statistical analysis of particulate matter air pollution. More broadly, however, we feel that the CD has not succeeded in adequately conveying the statistical and scientific interpretation issues that are involved in drawing conclusions from such complex issues from large epidemiological data sets. The bulk of this review has concentrated on two such kinds of studies: the time series analyses of PM exposure and mortality in Section 4, and the cohort studies in Section 5. Both kinds of studies raise a number of common issues: how to combine data from a large number of cities, especially when there is spatial dependence; the possibility of threshold effects or, more generally, a nonlinear dose-response curve; and the issue of co-pollutants. There are also some specific issues for each kind of study. The time series studies appear to have been substantially affected by publication bias, at least on the basis of our comparison of results from the NMMAPS study (which we presume to be free of publication bias) with other published analyses in the literature. There is also the question of model selection bias, which has not received anywhere near adequate treatment in the epidemiological literature. Bayesian model averaging is a relatively new technique developed by statisticians, and while not free of potentially problematic assumptions of its own, does offer a possible route to deriving results without this kind of bias. On the side of the cohort studies, we feel that the very broad issues raised by the ecological nature of the studies still needs further discussion, though we recognize that the HEI-sponsored re-analysis introduced a number of important new methodological developments.

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Comments on Chapter 6, Epidemiology:

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These comments are based in part on discussion in a reading group organized by the EPA Northwest Center for Particulate Air Pollution and Health at the University of Washington but they represent the opinions of the authors, not of the Center or the EPA.

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Overall comments:
The draft Air Quality Criteria for Particulate Matter appears to do a good job of collecting together most of the literature on associations between particle concentrations and health outcomes. However, the document omits a number of references that were in readily accessible parts of the scientific literature at the time of the review. These are predominantly, though not entirely, papers concerned with methodological issues. As we have only identified incorrect or missing citations of papers with which we have some personal connection we are concerned as to whether the accuracy of the remaining citations is similarly poor.

The chapter does not always distinguish clearly between summaries of the scientific literature and commentary on it. In addition, the commentary is fairly superficial in its examination of the design and methodology of the studies and how they fit together in answering the scientific and public health questions. This is true even in cases such as the HEI reanalysis project and NMMAPS where a substantial amount of expert review and commentary has been published.

In addition some of the commentary, particularly that included in the tables 6-16 and 6-17, appears to give criticism only of studies that do not find associations between particulate air pollution and health. Editorial commentary seems unnecessary in the tables, though a consistent summary of study design would be helpful. It is not even clear which statements in the table are taken from the paper and which are the opinions of the reviewer. In general the commentary in this chapter under-represents the potential for issues such as copollutants, measurement error, publication bias, and model selection to affect at least the magnitude of estimated health effects.

The chapter frequently refers to “consistency”, “coherence” or “homogeneity” without giving any definition of these terms or even indicating which of them are supposed to have a precise meaning. The extent of agreement between studies, and how it compares with the extent of agreement that would be expected given different study designs and conditions, is a very important question. It cannot be meaningfully addressed without at least some attempt to quantify extent of agreement.

The chapter also makes a number of references to plausible explanations for various observations in cases where the evidence to test these explanations is readily available. If these hypotheses are important they should be tested, if not they should be omitted. We have carried out two of these analyses, in Appendices A and B of our comments, and have indicated a number of other places in our specific comments where this could readily have been done.

In considering publication bias, model selection bias, effects of co-pollutants, and measurement error the authors conclude that each source of bias cannot on its own explain the observed associations between PM and health. This conclusion is entirely reasonable. However, they do not consider the problem of these sources acting together. For example, reasonable guesses about measurement error (in the absence of good data) suggest that it could not cause a truly null predictor to appear more significant than a real effect on health. It is less clear, however, that a modest association due to confounding could not be elevated to significance by measurement error and then appear consistent in the literature due to publication and model selection bias. Of course the reverse could also happen, and these combined biases could cause an important underestimate of the effects of PM. Presumably EPA cares about the magnitude, as well as the existence, of health effects; certainly the public and the scientific community are interested.

The issue of whether co-pollutants need to be included in health effects analyses, or if the analysis becomes cleaner when only one pollutant at the time is included in the analysis, is subject to substantial, and in our view very confused, discussion in the criteria document. It appears that the authors are arguing that since many different co-pollutants tend to be correlated, the uncertainty of the health effects estimates tend to cloud the conclusions. This is only the case if one assumes *a priori* that particulate matter must have an effect on health independently of other pollutants. This, however, is what the analyses discussed in the document are attempting to investigate, and the conclusions are far from clear-cut. The epidemiological evidence of the severity of fine particle health effects is simply not yet available: there is insufficient availability of PM2.5 data to draw any firm conclusions. There are several studies in which the PM effects disappear when other pollutants are included in the model. There are also several studies with the opposite result. If the reason for excluding multi-pollutant analysis is EPA’s need to set standards for specific pollutant measures then this should be made explicit. Even in this case the criteria document should discuss the co-pollutant problem more carefully.

It would be useful to state which associations have been seen at PM levels below the current standard and which have been seen only at higher levels. Given the difficulty of assessing nonlinearity, adverse effects seen in cities that are compliant with the current standard should have greater weight in considering tighter standards.

In our opinion, the most severe limitation of the evidence is that we do not yet have a firm grip on the composition of particulate matter in different parts of the United States. The criteria document authors seem to expect that health effects of particulate matter is a matter only of the size of the particles; not of the chemical composition of the particles. The variety of results with respect to co-pollutants can perhaps be caused by the variety of chemical compositions; this is certainly a plausible explanation of the regional variability found in the 90-cities study. The document does consider a few specific types of particle that have different typical sources, but a wider consideration of sources (diesel, gasoline, coal, vegetative burning, secondary reactions) would be beneficial.

In summary we feel that the chapter requires fairly major revision but that the bibliography requires much less revision. The chapter as it stands is not an adequate review of the scientific evidence. There is more commentary and opinion than is warranted for this document although overall it contains the information and references that would allow an adequate review to be made by a determined and knowledgeable reader.

Detailed comments:

p 6-2 11ff: The ordering of studies by increasing inferential strength conflicts sharply with established epidemiological usage. The attribution to Rothman and Greenland is incorrect. Those authors don't even discuss ecologic time series studies, their chapters on study design do not give any ordering of designs, nor does the term "inferential strength" even appear in their index.

It would be more appropriate to distinguish the types of effects of interest before attempting to order the study types in order of increasing inferential strength. Studies tuned to assessing the cumulative effects of exposure may not have much inferential strength for assessing acute exposure effects, and vice versa. Also omitted were other study designs such as intervention studies and case-crossover studies.

6-7 1-2: "some recent work suggests that time series data sets are also useful to examine responses to exposures over a longer time scale". This needs a reference

6-13 Table 6-1. This and the other tables would be easier to read with less text and perhaps more structured presentation of lags or typical concentrations of PM

6-18 Last column, The entry "SLC PM10 Total (0 d)" estimate gives only part of the confidence interval.

6-21 Levy paper: Is this paper appropriate to include as it was not in the peer-reviewed literature? The results quoted for total mortality: *5.6% (-2.4, 1.43) per 50 μg/ m^3*, cannot be correct as the estimate is not in the confidence interval.

6-49, 6.2.2.3.4.: "Consistency" has not been defined here. Confidence intervals (or posterior credible intervals for NMMAPS) should be given here as part of any definition.. How does the discussion of consistency match up with the NMMAPS conclusions of heterogeneity across regions when the regional estimates are also small and could appear to be similar the estimates that are claimed to be "consistent"? How is consistency defined when differences in measurement error, spatial variability, and other risk factors would be expected to cause variation in relative risks across different cities?

6-86 10 -- 6-87 3: The spatial dependence analysis done by the Reanalysis Team certainly deserves more than its brief mention in the CD. The existence of extensive expert commentary by the HEI scientific review board would appear to make a longer review relatively straightforward. The lack of balanced attention to reporting results of the Reanalysis Project makes the CD appear biased and not scientifically neutral.

6-88 1-2 "Education was used to index ... Physical activity and occupational exposure to dust were also used as covariate." These are not all the covariates that were examined. The covariates were used in models where they improved precision of the model or indicated effect modification. A large number of dietary and other life style covariates were evaluated for inclusion in the model according to those criteria. The method is explained in the Appendix of Abbey et al. (1999).

6-88 12-18 Cardiopulmonary results are discussed in this sentence, but the RR referred to is not correct for cardiopulmonary as underlying cause (the reported relative risk was actually 1.14, 95% CI 1.03-1.56 for 30days/yr > 100 mg/m3 PM10). In addition, sensitivity analyses were not done for cardiopulmonary mortality, but `contributing respiratory cause' (CRC) mortality. On the other hand Table 6-8 has correct cardiopulmonary results, not CRC mortality. The chapter needs to distinguish more carefully between these.

6-89 7-8, "For example, if the male spent . . ." If time outdoors were to explain these effects the penetration of outdoor PM into the indoor environment would have to be quite low. This disagrees with the measurement error discussion in section 6.4.7, where a value of 0.60 is used.

6-89 13 "The AHSMOG cancer analyses showed a confusing array of results for lung cancer mortality (Table 6-9)." The results are only confusing when summarized entirely in terms of statistical significance. The small numbers of events make this sort of summary inappropriate, and the confidence intervals given in Table 6-8 are less confusing.

6-94 3-6. "Overall, . . . do not find consistent statistically significant association. . ." The word "consistent" needs to be clarified, as in many other parts of the document. The

AHSMOG results were consistent with a harmful effect of PM10, and some of the results were also consistent with zero effect, in the statistical sense.

6-94, line 9. TSP was only used to estimate PM10 only part of the study period (1977-1987). Measured PM was used for the remainder.

6.2.3.2.2 The short-term vs. long term effects analysis in the AHSMOG study (included in McDonnell et al. (2000)) were not mentioned.

6-112ff, 6-144ff In Tables 6-16 and 6-17 there are critical comments on the methodology exclusively in those papers that do not find significant effects. This is certainly not due to impeccable methodology in the other studies.

6-142 17-20: The exclusion of multipollutant analyses from consideration due to concerns about multicollinearity does not give a balanced approach to the issue. Multicollinearity means that it is difficulty to establish the effects of PM separately from, say, CO, but not that this problem can be ignored. Also, as section 6.1.2 admitted, the copollutants need not merely be confounders but may be effect modifiers.

An alternate approach is to estimate an "air pollution" effect that would account for the joint change in several pollutants simultaneously. A joint effect estimate will not have the same multicollinearity concerns and will allow for more balance in the Criteria Document by entertaining the possibility that the toxic component of air pollution may not be best measured by PM alone.

6-143 25-30: This perspective does not consider the effects of model selection bias. Caution should be used in systematically picking the most positively significant pollutant coefficient as was demonstrated by Lumley and Sheppard (2000).

6-149 Norris et al. (2000): The Seattle component of this analysis was included to focus on the stagnation persistence index in a second city and not as a new analysis per se. The data are essentially identical to the Norris et al. (1999) analysis so these two papers should not be treated separately with respect to the Seattle analysis.

6-153 Lumley and Heagerty (1999) This study should not be included in this table. The data are the same as those analysed by Sheppard et al (1999) and so are already in the table. The analysis was used solely to demonstrate the properties of a new statistical estimator. It was not intended as a definitive analysis of PM health effects, as the paper itself clearly states.

6-155 Sheppard et al. (1999): The description of the numbers of sites for different pollutants is incorrect. There were 3 PM sites, 4 CO sites, and one site each for SO_2 and O_3. Only 2 sites measured $PM_{2.5}$.

6-172 4-7: Speculation on this point is unnecessary. This statement can be verified very easily using the data in Appendices 6A-1 and 6A-2. In fact while least squares linear regression analysis indicates a positive association between population size and mean PM_{10} levels, inspection of the relationship shows that this is driven by a few large cities that are highly influential in the analysis. There are many smaller cities with higher average PM_{10} levels than experienced in the largest cities. (See plot in Appendix I.)

6-175 7-14: See comments on Lumley and Heagerty (1999) above. They used the same data as Sheppard, and did not aim to present a definitive reanalysis.

6-175 24-25: The Norris et al. (1999) paper used Emergency Department visits, not hospital admissions.

6-177 27 – 6-178 5: These comments are at best confusingly presented. As in all the other analyses described in this report the studies of children have presented relative risks rather than absolute risk differences or differences in numbers of events. It is true than the absolute increase in an individual child's risk is greater than in an individual healthy adult's risk However, it is not clear than the base rate is higher in children than in the susceptible adults that have been the focus of research (and no evidence is given for this). In addition, the same argument could be extended by pointing out that there are far fewer infants than adults, so the number of adverse events caused by a 1.05 relative risk in infants will be less than the number of adverse events caused by the same relative risk in adults.

6-182 Figure 6-7: The two papers by Norris et al., include the same Seattle analysis, as mentioned above in comments for 6-149. Only one of them should appear.

6-189ff Table 6-20. Yu et al., (2000) should be included here, a fairly large panel study of acute effects on symptoms in asthmatic children

6-216 30: The comment that a majority of studies show statistically significant results is not a useful summary. There is no reason to expect consistency in p-values across studies, nor is this evidence of consistency in results, particularly given risks of publication bias and model selection bias.

6-217 22 – 6-218 18: The fact that there exist many equally plausible models for a given set of data is precisely that which is addressed by the research on model selection that is largely neglected by this chapter. Specifically, attention needs to be given to Clyde (2000), who used methods for summarizing the conclusions of vast collections of possible models. Also related is the work of Lumley and Sheppard (2000) who showed that selecting the most favorable of just seven possible models could produce biases of the same order of magnitude as the observed PM effects. See also the evidence of model selection and publication bias that can be inferred from the studies cited in Table 6-1 by using the NMMAPS result as a gold standard, described in detail in our Appendix II.

6-218 22-23: It seems that some minimal level of evaluation and scrutiny is necessary. This should be stated (e.g. only papers published in peer-reviewed journals).

6-220 bottom and 6-226, section 6.4.2.3.: Must the attention continue on single pollutants in isolation of the other pollutants also in the atmosphere? Assessment of an air pollution effect may be a more fruitful approach. The simultaneous inclusion of multiple pollutants in a model can be handled fruitfully by estimating the joint effect of a change in several pollutants simultaneously. This was done in a time series analysis by Sheppard et al. (1999) and in a panel study by Yu et al, (2000). The same comments also apply to 6-268 24 ff.

6-227 8-14: The Norris et al. (2000) paper should be included in this list.

6-236 22-28: See comments on Lumley and Heagerty (1999) above.

6-238 26-27: This sentence must be rewritten. Not only does it ignore peer-reviewed published literature on model selection bias in the air pollution epidemiology literature (Clyde (2000), Lumley and Sheppard (2000)), but it also ignores the accumulating evidence in the literature that would limit the number of lags under consideration to only the few lags relatively close to the event. It is important to recognize that after a first initial few hypothesis-generating studies, new work should focus on hypothesis testing and confirmation of the results of earlier studies. Thus continual exploration of the lag structure in each new analysis is not justified and can lead to systematic positive bias. See further analysis below (Appendix II) on the evidence of publication bias in the Criteria Document.

6-243 11-12: Certainly other arguments are equally plausible.

6-249 24 – 6-250 21: The measurement error discussion, and in particular the comments at 6-250 1-2 “a condition not demonstrated as occurring in actual air pollution data sets” mask the fact that there are not yet sufficient data to make any conclusive assessments of measurement error. In particular, the data on personal exposure to pollution of ambient origin, the key error component in the Zeger et al. analysis, are very limited even for particle concentrations. There are virtually no data on the magnitudes and correlations of this source of exposure error for multiple pollutants.

6-256 Section 6.4.8.2.: The discussion of case-crossover analyses omits at least two papers, a report from HEI (Checkoway et al (2000)) and a methodological paper by Lumley and Levy (2000). The Checkoway et al. report contained, in addition to analyses of acute associations with primary cardiac arrest (citted on 6-132 but not here), substantial simulations that prompted the mathematical investigation of Lumley & Levy.

6-259 3-7: The chapter states that “much homogeneity appeared to exist across various geographic locations”. The NMMAPS analysis in fact came to the opposite conclusion, that there was significant heterogeneity. Given this disagreement there needs to be a precise definition of “homogeneity” so that evidence can be adduced for or against this statement.

6-260 18-19. ‘Data … were optically scanned and digitized’ suggests that access to the correct data was not sought or was refused. Either possibility would be disturbing.

6-263 20-21: Define “near the national mean”. From the graph on 6-262 it appears that in addition to the two cities with very much lower effect estimates there is one city with close to twice the national mean estimate, leaving three of the six that are arguably “close”.

6-263 29 – 6-264 2: There are sufficient data in the Criteria Document to do these calculations. Cursory inspections and speculation should be omitted from the Criteria Document. If these calculations are of genuine interest they should be performed, otherwise they should be omitted.

6-265 24: As commented above on a number of similar occasions, there is no definition of “considerable degree of coherence” given that would allow there to be any evidence for or against this statement. It is not trivial to decide what degree of coherence can be expected or to evaluate the evidence that such a degree has been attained. Also 6-267 23.

6-266 20: Define “meaningful heterogeneity”. Compare this with definitions of the other terms (consistency, homogeneity, coherence).

Additional Bibliography

Clyde M (2000). “Model uncertainty and health effect studies for particulate matter” *Environmetrics* 11:745-763

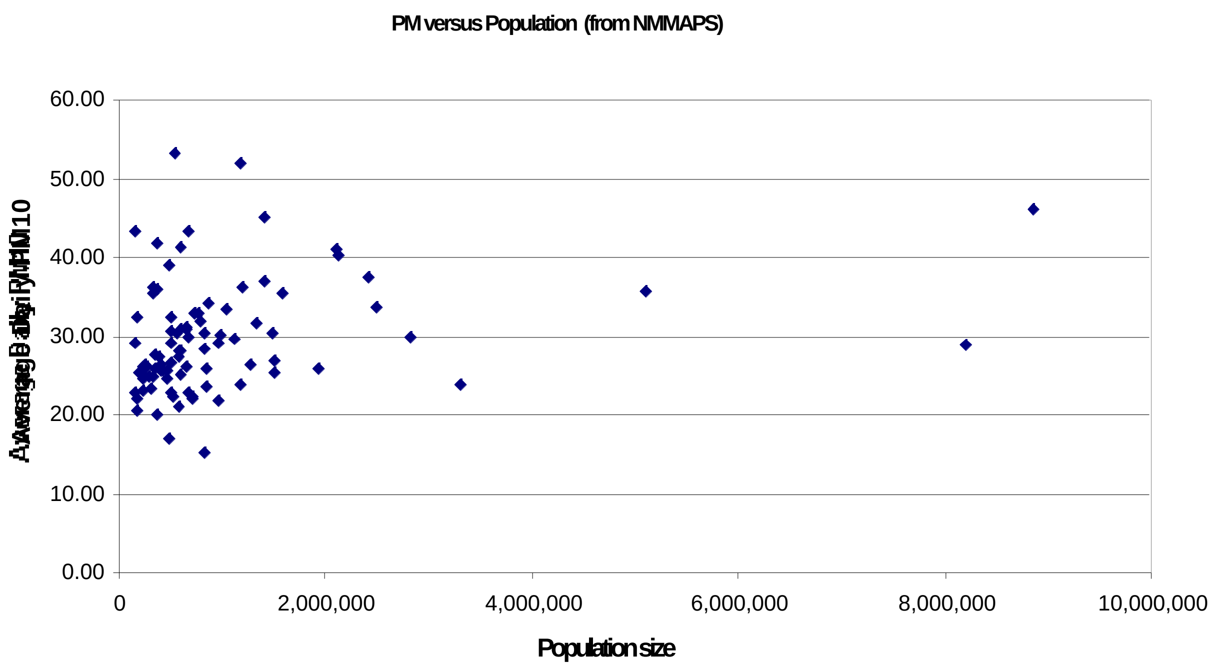
Lumley T, Levy D, Lumley T, Levy D (2000) "Bias in the case-crossover design: implications for studies of air pollution" *Environmetrics* 11: 689-704

Lumley T, Sheppard L (2000) "Assessing seasonal confounding and model selection bias in air pollution epidemiology using positive and negative control analyses" *Environmetrics* 11:705-717

Yu O, Sheppard L, Lumley T, Koenig JQ, Shapiro GG (2000) "Effects of ambient air pollution on symptoms of asthma in Seattle-area children" *Environmental Health Perspectives* 108:1209-1214.

Appendix I

See comments for 6-172 4-7. This plot shows the relationship between PM10 and population that is hypothesis in the chapter. It also shows that there is a lot of variability in this relationship. While larger cities tend to have higher PM10 there are many small cities with high PM10 and fairly large ones with low PM10.



Appendix II

In section 6.4.4 (lines 26, 27 of p. 6-238), the Criteria Document explicitly claims that it is reasonable to select the most significant lag among a set of possible lags even though such a practice may bias the chance of finding a significant association. This statement is made in spite of evidence of model selection bias that results from this approach in the peer-reviewed literature (see the specific study examined by Lumley and Sheppard, 2000; see below for further comment) and evidence to the contrary that can be compiled from studies reviewed in the Criteria Document alone. We now present an analysis of data from the Criteria Document that indicates the presence of selection bias in the published literature.

The NMMAPS study can be used as a gold standard against which to assess the presence of publication bias in other PM mortality effect analyses. Among the strengths of NMMAPS relevant for an analysis of publication bias, the data were consistently handled across all cities, city-specific models were specified using the same criteria in each city, and the cities to be included were not specifically selected based on outcome (size is a covariate, not an outcome). We compare the compilation of city-specific results from NMMAPS with estimates reported in 21 separate references in Table 6-1. To be eligible for this analysis, the paper had to report a total mortality effect estimate for a 50 _g/m^3 increment of PM_{10} and reside in the peer-reviewed literature. (In our opinion, Levy (1998) was not peer-reviewed and therefore we excluded it.) All the estimates considered were city-specific with the exception of the Schwartz (2000) 10-city estimate and the Burnett (1998) 8-city estimate. A table with the included studies, cities, statistical significances (as indicated by the confidence interval), and effect estimates gleaned from Table 6-1 is attached. We test the null hypothesis that there is no difference between the NMMAPS collection of results and the independently published set. We can test this hypothesis in two ways: by looking at statistical significance of the results and by considering positive point estimates of excess deaths. In NMMAPS, 11 out of 88 city-specific estimates were statistically significant and 63 out of 88 gave positive point estimates for excess deaths. In contrast, out of the 24 separate confidence intervals reported in the 21 references, 19 out of 24 were statistically significant. This leads to a z-statistic of 7.29 and resoundingly rejects the null hypothesis of no difference. Similarly, of the 28 separate effect estimates reported, 26 were positive, leading to a z-statistic of 3.09 for this comparison. Again the null hypothesis of no difference is rejected. Thus by relying only on information summarized in the Criteria Document, it is reasonable to conclude that the statement on page 6-238 (lines 26-27) is inappropriate.

Studies Including PM_{10} Mortality Estimates

First author and publication date	City	Statistical significance	Estimate for 50 _g/m^3 PM_{10}
Schwartz (2000a)	10 cities	Sig	3.4
Moolgavkar (2000a)	Cook County	-	.5-1
Moolgavkar (2000a)	Maricopa County	-	.25-1
Moolgavkar (2000a)	LA	-	.5
Ostro (1999a)	Cochella Valley	Sig	4.6
Ostro (1999a)	Cochella Valley	NS	2.0
Fairley (1999)	Santa Clara County	-	8
Pope (1999a)	Ogden	Sig	12
Pope (1999a)	Salt Lake City	Sig	2.3
Pope (1999a)	Provo	NS	1.9
Schwartz (2000)	Chicago	Sig	4.5
Lipmann (2000)	Detroit	NS	4.4
Gwynn (2000)	Buffalo	Sig	12
Mar (2000)	Pheonix	Sig	5.4
Tsai (2000)	Newark	Sig	5.7
Tsai (2000)	Camden	NS	11.1
Tsai (2000)	Elizabeth	NS	-4.9
Gamble (1998)	Dallas	NS	-3.6
Burnett (1998a)	8 Canadian Cities	Sig	3.5
Burnett (1998a)	Toronto	Sig	3.5
Wordley (1997)	Birmingham UK	Sig	5.6
Hoek (2000)	Netherlands	Sig	0.9
Ponka (1998)	Helsinki	Sig	18.8
Peters (1999a)	Czech Republic	Sig	4.8
Michelozzi (1998)	Rome	Sig	1.9
Wichmann (2000)	Frankfurt	Sig	6.6
Morgan (1998)	Sydney	Sig	4.7
Ostro (1998)	Bangkok	Sig	5.1